IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Susanne MATHEUS et al. Examiner: KAUFMAN, CLAIRE M

Serial No.: 10/588,458 Group Art Unit: 1646

Filed: August 4, 2006 Confirmation No.: 5757

Title: **HIGHLY CONCENTRATED, LIQUID FORMULATIONS OF ANTI-EGFR ANTIBODIES**

REPLY BRIEF

Mail Stop **Appeal Brief- Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Supplemental Reply Brief is submitted under 37 C.F.R. §41.41 in response to the Examiner's Answer mailed May 3, 2010.

1. Rejections withdrawn:

(None)

2. Rejections maintained:

The rejection of claims 1, 4, 8, 11, 16, 17 and 21-24 under 35 USC §103(a) as allegedly unpatentable over Sridhar (Lancet Oncology, 2003) in view Arvinte et al. (WO 02/96457) has been sustained.

The rejection of claims 1-3, 5-10 and 12-17 under the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1–13, 15-24 and 26–27 of Mahler's US application no. 10/996,597 (*hereinfafter* "the '597 application") in view Lam's US patent no. 6,171,586 (*hereinafter* "the '586 patent") has been sustained. The following arguments are provided to rebut the assertions made in the Examiner's Answer regarding the obviousness-type double patenting rejection.

The Examiner continues to contend that Mahler's disclosure of c225 and h425 antibody

formulations coupled with Lam's generic teaching of concentrated antibody formulations *prima facie* renders obvious the claims of the instant application. To this end, the Examiner concedes that the disclosure in the Examples section of the '586 patent is limited to anti-CD18 and anti-CD20 antibody formulations and that Lam is silent with respect to the c225 and h425 antibodies of the instant application. Also, the concentration ranges recited in Applicants' claims are outside what is taught by the cited references. However, the Office Action proceeds to allege that the '597 application teaches anti-EGFR antibody formulations containing 0.1 mg/ml - 50 mg/ml of the antibody and that the disclosure in the '586 patent on "*a generically applicable* method of making a stable concentrated antibody formulations" prima facie renders obvious the claims of the instant application. The Office Action further states that it would be obvious to use Mahler's c225 and h425 antibodies to make Lam's formulations. See page 5 of the Office Action. Applicants respectfully disagree with this assertion.

With respect to the concentration of the antibody molecules in the formulations, Mahler teaches that anti-EGFR antibody in the formulation is at a concentration of from 0.1 mg/ml to 50 mg/ml, preferably from 2 mg/ml to 10 mg/ml, particularly preferably about 5 mg/ml. See, paragraphs [0019] to [0022] of Mahler's published US application (US pub. No. 2005-0175611). Mahler fails to teach or suggest the concentration ranges recited in Appellants' claims. Lam is also silent regarding the concentration ranges recited in Applicants' claims. Like the primary Lam reference, the preferred embodiments in Mahler are directed to antibodies that are formulated at a lower concentration than the formulations claimed herein. See the entire Examples section. Mahler does not provide any hint or suggestion that the recited anti-EGFR antibodies of the present invention (i.e., Mab c225 or Mab h425) can be prepared as highly concentrated formulations (50 mg/ml to 180 mg/ml). This distinction is further elucidated in the descriptive portion of Appellants' specification. See, for example, paragraph [0012] of the published US application (US pub. No. 2007-0172475) and **claim 11**. Accordingly, Mahler in view of Lam fails to render obvious the claims of the instant application. See MPEP §2144.05. Favorable action is respectfully requested.

With respect to "generic applicability" of methods for making stably concentrated antibody formulations, Applicants note that the disclosure in the '586 patent, which the USPTO relies on, itself teaches refutes the PTO's assertions. In accordance with the Examples of the Lam patent, stable "aqueous formulation for [0.5–25 mg/mL] rhuMAb CD18 is **10 mM sodium acetate**, 8% trehalose wN, 0.01% TWEEN 20™, pH 5.0" while stable prototype liquid

multidose formulation of rhuMAb CD20 contains "40 mg/mL rhuMAb CD20, **25 mM acetate**, 150 mM trehalose, 0.9% benzyl alcohol, 0.02% polysorbate 20 at pH 5.0." It is clear from Lam's disclosure that compared to MAbCD20, stable formulations of the CD18 monoclonal antibody can be prepared with reduced concentrations of the acetate buffer and polysorbate (i.e., TWEEN20) and without benzyl alcohol. There is no generic method for preparing the antibody formulations, but rather, specific components and conditions have to be employed. The reasoning is provided in the BACKGROUND section of Lam et al., wherein it is explicitly stated that "because proteins are larger and more complex than traditional organic and inorganic drugs (i.e., possessing multiple functional groups in addition to complex three-dimensional structures), the formulation of such proteins poses special problems." The Tables in the Examples section outline numerous variables, e.g., antibody concentrations, buffer types, buffer concentrations, salt types, salt concentrations, pH, isotonicity modifiers, surfactants and polysorbates, that are to be optimized for preparing stable formulations. Accordingly, the skilled artisan would note that MAbCD20 of Lam is not equivalent to, but rather quite different from MAbc225 of Mahler et al. They are not simple substitutions of one another. Accordingly, the antibody preparations, compositions, kits of the present invention, including methods for obtaining such are not rendered obvious by Mahler and Lam. Favorable reconsideration is respectfully requested.

For the above reasons and the reasons set forth in Appellants' Brief, it is submitted that the decision of the Examiner finally rejecting claims 1-3, 5-10 and 12-17, on appeal, is in error and should be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

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Attorney Docket No.: MERCK-3217

Date: July 6, 2010